CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 064125

Trade Name : STERILE CEFUROXIME SODIUM USP

Generic Name: Sterile Cefuroxime Sodium USP, 750mg(base)/vial and 1.5Gm (base)/vial

Sponsor : G. C. Hanford Manufacturing Company

Approval Date: May 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 064125

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 064125

APPROVAL LETTER

AADA 64-125

G.C. Hanford Manufacturing Company
Attention: Carl E. Fuller
304 Oneida Street
P.O. Box 1017
Syracuse, NY 13201

Dear Sir:

This is in reference to your abbreviated antibiotic application dated March 31, 1994, submitted pursuant to Section 507 of the Food, Drug, and Cosmetic Act, for Sterile Cefuroxime Sodium USP, 750 mg (base)/vial and 1.5 g (base)/vial.

Reference is also made to your amendments dated January 19, August 29 and October 15, 1996; and January 23 and May 20, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Sterile Cefuroxime Sodium, USP 750 mg (base)/vial and 1.5 (base)/vial, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zinacef® 750 mg (base)/vial and 1.5 g (base)/vial of Glaxo Wellcome, Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any changes in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

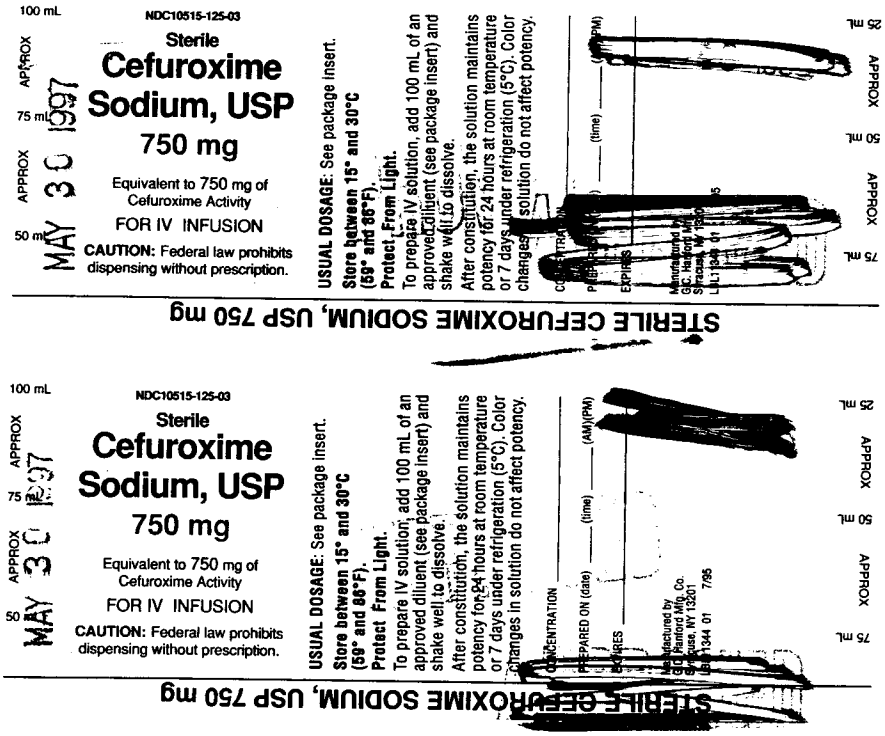
/S/ 7/30/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

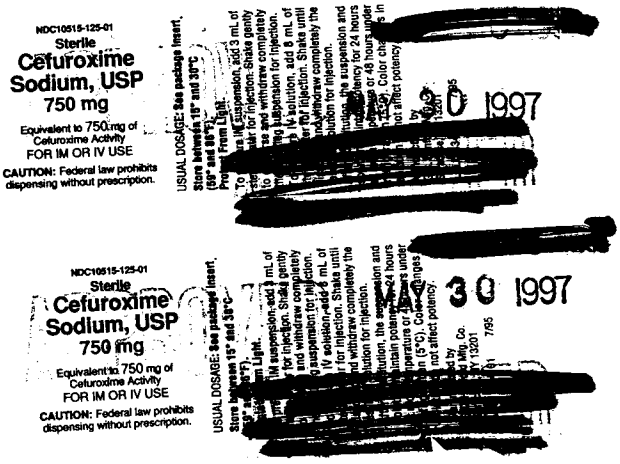
APPLICATION NUMBER 064125

FINAL PRINTED LABELING


100 mL
NDC10515-125-03
Sterile
Cefuroxime
Sodium, USP
750 mg
Equivalent to 750 mg of
Cefuroxime Activity
FOR IV INFUSION
CAUTION: Federal law prohibits
dispensing without prescription.
USUAL DOSAGE: See package insert.
Store between 15° and 30°C
(59° and 86°F).
Protect From Light.
To prepare IV solution, add 100 mL of an
approved diluent (see package insert) and
shake well to dissolve.
After constitution, the solution maintains
potency for 24 hours at room temperature
or 7 days under refrigeration (5°C). Color
changes in solution do not affect potency.
CONCENTRATION
PREPARED ON (date) (time) (AM)(PM)
EXPIRES
Manufactured by
GD, Hanford Mfg. Co.
Syracuse, NY 13201
LILLY 1344 01 7/95
APPROX 25 mL
APPROX 50 mL
APPROX 75 mL
APPROX 75 mL
APPROX 50 mL
APPROX 25 mL
MAY 30 1997
STERILE CEFUROXIME SODIUM, USP 750 mg

100 mL
NDC10515-125-03
Sterile
Cefuroxime
Sodium, USP
750 mg
Equivalent to 750 mg of
Cefuroxime Activity
FOR IV INFUSION
CAUTION: Federal law prohibits
dispensing without prescription.
USUAL DOSAGE: See package insert.
Store between 15° and 30°C
(59° and 86°F).
Protect From Light.
To prepare IV solution, add 100 mL of an
approved diluent (see package insert) and
shake well to dissolve.
After constitution, the solution maintains
potency for 24 hours at room temperature
or 7 days under refrigeration (5°C). Color
changes in solution do not affect potency.
CONCENTRATION
PREPARED ON (date) (time) (AM)(PM)
EXPIRES
Manufactured by
GD, Hanford Mfg. Co.
Syracuse, NY 13201
LILLY 1344 01 7/95
APPROX 25 mL
APPROX 50 mL
APPROX 75 mL
APPROX 75 mL
APPROX 50 mL
APPROX 25 mL
MAY 30 1997
STERILE CEFUROXIME SODIUM, USP 750 mg

7


NDC10515-125-01
Sterile
Cefuroxime
Sodium, USP
750 mg
Equivalent to 750 mg of
Cefuroxime Activity
FOR IM OR IV USE
CAUTION: Federal law prohibits
dispensing without prescription.
USUAL DOSAGE: See package insert.
Store between 15° and 30°C
(59° and 86°F).
Protect From Light.
MAY 30 1997
NDC10515-125-01
Sterile
Cefuroxime
Sodium, USP
750 mg
Equivalent to 750 mg of
Cefuroxime Activity
FOR IM OR IV USE
CAUTION: Federal law prohibits
dispensing without prescription.
MAY 30 1997

INS11339 01
February 1996

Sterile
Cefuroxime Sodium, USP
FOR INTRAMUSCULAR OR INTRAVENOUS INJECTION

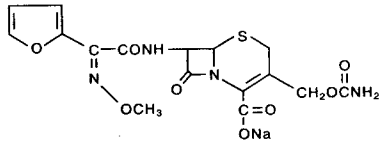
[redacted]

MAY 30 1997

[redacted]

DESCRIPTION

Sterile cefuroxime sodium, USP is a sterile, semisynthetic, broad-spectrum, cephalosporin antibiotic for intravenous or intramuscular administration. Chemically, it is the sodium salt of (6R,7R)-3-carbamoyloxymethyl-7-[Z-2-methoxyimino-2-(fur-2-yl)acetamido] ceph-3-em-4-carboxylate, and has the following structural formula:



The molecular formula is $C_{16}H_{15}N_4NaO_8S$. The molecular weight is 446.37.

Sterile cefuroxime sodium, contains approximately 54.2 mg (2.4 mEq) of sodium per gram of cefuroxime activity.

Sterile cefuroxime sodium, in sterile crystalline form is supplied in vials equivalent to 750 mg or 1.5 g of cefuroxime as cefuroxime sodium. Solutions of sterile cefuroxime sodium, range in color from light yellow to amber, depending on the concentration and diluent used. The pH of freshly constituted solutions usually ranges from 6 to 8.5.

CLINICAL PHARMACOLOGY

After intramuscular (IM) injection of a 750 mg dose of cefuroxime to normal volunteers, the mean peak serum concentration was 27 mcg/mL. The peak occurred at approximately 45 minutes (range, 15 to 60 minutes). Following IV doses of 750 mg and 1.5 g, serum concentrations were approximately 50 and 100 mcg/mL, respectively, at 15 minutes. Therapeutic serum concentrations of approximately 2 mcg/mL or more were maintained for 5.3 hours and 8 hours or more, respectively. There was no evidence of accumulation of cefuroxime in the serum following IV administration of 1.5 g doses every 8 hours to normal volunteers. The serum half-life after either IM or IV injections is approximately 80 minutes.

Approximately 89% of a dose of cefuroxime is excreted by the kidneys over an 8-hour period, resulting in high urinary concentrations.

Following the IM administration of a 750 mg single dose, urinary concentrations averaged 1,300 mcg/mL during the first 8 hours. Intravenous doses of 750 mg and 1.5 g produced urinary levels averaging 1,150 and 2,500 mcg/mL, respectively, during the first 8-hour period.

The concomitant oral administration of probenecid with cefuroxime slows tubular secretion, decreases renal clearance by approximately 40%, increases the peak serum level by approximately 30%, and increases the serum half-life by approximately 30%. Cefuroxime is detectable in therapeutic concentrations in pleural fluid, joint fluid, bile, sputum, bone, cerebrospinal fluid (in patients with meningitis), and aqueous humor.

Cefuroxime is approximately 50% bound to serum protein.

Microbiology: Cefuroxime has *in vitro* activity against a wide range of gram-positive and gram-negative organisms, and it is highly stable in the presence of beta-lactamases of certain gram-negative bacteria. The bactericidal action of cefuroxime results from inhibition of cell-wall synthesis.

Cefuroxime is usually active against the following organisms *in vitro*.

Aerobes, Gram-positive: *Staphylococcus aureus; Staphylococcus epidermidis; Streptococcus pneumoniae;* and *Streptococcus pyogenes* (and other streptococci). NOTE: Most strains of enterococci, e.g., *Enterococcus faecalis* (formerly *Streptococcus faecalis*), are resistant to cefuroxime. Methicillin-resistant staphylococci and *Listeria monocytogenes* are resistant to cefuroxime.

Aerobes, Gram-negative: *Citrobacter* spp; *Enterobacter* spp; *Escherichia coli; Haemophilus influenzae* (including ampicillin-resistant strains); *Haemophilus parainfluenzae; Klebsiella* spp (including *Klebsiella pneumoniae*); *Moraxella (Branhamelia) catarrhalis* (including ampicillin- and cephalothin-resistant strains); *Morganella morganii* (formerly *Proteus morganii*); *Neisseria gonorrhoeae* (including penicillinase- and non-penicillinase-producing strains); *Neisseria meningitidis; Proteus mirabilis; Providencia rettgeri* (formerly *Proteus rettgeri*); *Salmonella* spp; and *Shigella* spp.

NOTE: Some strains of *Morganella morganii, Enterobacter cloacae,* and *Citrobacter* spp have been shown by *in vitro* tests to be resistant to cefuroxime and other cephalosporins. *Pseudomonas* and *Campylobacter* spp, *Acinetobacter calcoaceticus,* and most strains of *Serratia* spp and *Proteus vulgaris* are resistant to most first- and second-generation cephalosporins.

Anaerobes: Gram-positive and gram-negative cocci (including *Peptococcus* and *Peptostreptococcus* spp); gram-positive bacilli (including *Clostridium* spp); and gram-nega-

Microbiology: Cefuroxime has *in vitro* activity against a wide range of gram-positive and gram-negative organisms, and it is highly stable in the presence of beta-lactamases of certain gram-negative bacteria. The bactericidal action of cefuroxime results from inhibition of cell-wall synthesis.

Cefuroxime is usually active against the following organisms *in vitro*.

Aerobes, Gram-positive: *Staphylococcus aureus; Staphylococcus epidermidis; Streptococcus pneumoniae;* and *Streptococcus pyogenes* (and other streptococci). NOTE: Most strains of enterococci, e.g., *Enterococcus faecalis* (formerly *Streptococcus faecalis*), are resistant to cefuroxime. Methicillin-resistant staphylococci and *Listeria monocytogenes* are resistant to cefuroxime.

Aerobes, Gram-negative: *Citrobacter* spp; *Enterobacter* spp; *Escherichia coli; Haemophilus influenzae* (including ampicillin-resistant strains); *Haemophilus parainfluenzae; Klebsiella* spp (including *Klebsiella pneumoniae*); *Moraxella (Branhamelia) catarrhalis* (including ampicillin- and cephalothin-resistant strains); *Morganella morganii* (formerly *Proteus morganii*); *Neisseria gonorrhoeae* (including penicillinase- and non-penicillinase-producing strains); *Neisseria meningitidis; Proteus mirabilis; Providencia rettgeri* (formerly *Proteus rettgeri*); *Salmonella* spp; and *Shigella* spp.

NOTE: Some strains of *Morganella morganii, Enterobacter cloacae,* and *Citrobacter* spp have been shown by *in vitro* tests to be resistant to cefuroxime and other cephalosporins. *Pseudomonas* and *Campylobacter* spp, *Acinetobacter calcoaceticus,* and most strains of *Serratia* spp and *Proteus vulgaris* are resistant to most first- and second-generation cephalosporins.

Anaerobes: Gram-positive and gram-negative cocci (including *Peptococcus* and *Peptostreptococcus* spp); gram-positive bacilli (including *Clostridium* spp); and gram-negative bacilli (including *Bacteroides* and *Fusobacterium* spp).

NOTE: *Clostridium difficile* and most strains of *Bacteroides fragilis* are resistant to cefuroxime.

Susceptibility Tests: ***Diffusion Techniques:*** Quantitative methods that require measurement of zone diameters give an estimate of antibiotic susceptibility. One such standard procedure[1] that has been recommended for use with discs to test susceptibility of organisms to cefuroxime uses the 30-mcg cefuroxime disc. Interpretation involves the correlation of the diameters obtained in the disc test with the minimum inhibitory concentration (MIC) for cefuroxime.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Moderately Susceptible" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high antibiotic levels are attained. A report of "Intermediate" suggests an equivocable or indeterminate result. A report of "Resistant" indicates that achievable concentrations of the antibiotic are unlikely to be inhibitory and other therapy should be selected.

Reports from the laboratory giving results of the standard single-disc susceptibility test for organisms other than *Haemophilus* spp and *Neisseria gonorrhoeae* with a 30-mcg cefuroxime disc should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥18	(S) Susceptible
15–17	(MS) Moderately Susceptible
≤14	(R) Resistant

Results for *Haemophilus* spp should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥24	(S) Susceptible
21–23	(I) Intermediate
≤20	(R) Resistant

Results for *Neisseria gonorrhoeae* should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥31	(S) Susceptible
26–30	(MS) Moderately Susceptible
≤25	(R) Resistant

Organisms should be tested with the cefuroxime disc since cefuroxime has been shown by *in vitro* tests to be active against certain strains found resistant when other beta-lactam discs are used. The cefuroxime disc should not be used for testing susceptibility to other cephalosporins.

Standardized procedures require the use of laboratory control organisms. The 30-mcg cefuroxime disc should give the following zone diameters.

1. Testing for organisms other than *Haemophilus* spp and *Neisseria gonorrhoeae:*

Organism	Zone Diameter (mm)
Staphylococcus aureus ATCC 25923	27–35
Escherichia coli ATCC 25922	20–26

2. Testing for *Haemophilus* spp:

Organism	Zone Diameter (mm)
Haemophilus influenzae ATCC 49766	28–36

3. Testing for *Neisseria gonorrhoeae:*

Organism	Zone Diameter (mm)
Neisseria gonorrhoeae ATCC 49226	33–41
Staphylococcus aureus ATCC 25923	29–33

Dilution Techniques: Use a standardized dilution method[1] (broth, agar, microdilution) or equivalent with cefuroxime powder. The MIC values obtained for bacterial isolates other than *Haemophilus* spp and *Neisseria gonorrhoeae* should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤8	(S) Susceptible
16	(MS) Moderately Susceptible
≥32	(R) Resistant

MIC values obtained for *Haemophilus* spp should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤4	(S) Susceptible
8	(I) Intermediate
≥16	(R) Resistant

MIC values obtained for *Neisseria gonorrhoeae* should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤1	(S) Susceptible
2	(MS) Moderately Susceptible
≥4	(R) Resistant

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard cefuroxime powder should provide the following MIC values.

criteria:

MIC (mcg/mL)	Interpretation
≤4	(S) Susceptible
8	(I) Intermediate
≥16	(R) Resistant

MIC values obtained for *Neisseria gonorrhoeae* should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤1	(S) Susceptible
2	(MS) Moderately Susceptible
≥4	(R) Resistant

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard cefuroxime powder should provide the following MIC values.

1. For organisms other than *Haemophilus* spp and *Neisseria gonorrhoeae:*

Organism	MIC (mcg/mL)
Staphylococcus aureus ATCC 29213	0.5–2.0
Escherichia coli ATCC 25922	2.0–8.0

2. For *Haemophilus* spp:

Organism	MIC (mcg/mL)
Haemophilus influenzae ATCC 49766	0.25–1.0

3. For *Neisseria gonorrhoeae:*

Organism	MIC (mcg/mL)
Neisseria gonorrhoeae ATCC 49226	0.25–1.0
Staphylococcus aureus ATCC 29213	0.25–1.0

INDICATIONS AND USAGE

Sterile cefuroxime sodium, is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. **Lower Respiratory Tract Infections,** including pneumonia, caused by *Streptococcus pneumoniae* , *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* spp, *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing strains), *Streptococcus pyogenes,* and *Escherichia coli.*
2. **Urinary Tract Infections** caused by *Escherichia coli* and *Klebsiella* spp
3. **Skin and Skin Structure Infections** caused by *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing strains), *Streptococcus pyogenes, Escherichia coli, Klebsiella* spp, and *Enterobacter* spp
4. **Septicemia** caused by *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing strains), *Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae* (including ampicillin-resistant strains), and *Klebsiella* spp
5. **Meningitis** caused by *Streptococcus pneumoniae, Haemophilus influenzae* (including ampicillin-resistant strains), *Neisseria meningitidis, Staphylococcus aureus* (penicillinase- and non-penicillinase-producing strains).
6. **Gonorrhea:** Uncomplicated and disseminated gonococcal infections due to *Neisseria gonorrhoeae* (penicillinase- and non-penicillinase-producing strains) in both males and females.
7. **Bone and Joint Infections** caused by *Staphylococcus aureus* (including penicillinase- and non-penicillinase-producing strains).

Clinical microbiological studies in skin and skin structure infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. Cefuroxime has been used successfully in these mixed infections in which several organisms have been isolated. Appropriate cultures and susceptibility studies should be performed to determine the susceptibility of the causative organisms to cefuroxime.

Therapy may be started while awaiting the results of these studies; however, once these results become available, the antibiotic treatment should be adjusted accordingly. In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, cefuroxime may be used concomitantly with an aminoglycoside (see **PRECAUTIONS**). The recommended doses of both antibiotics may be given depending on the severity of the infection and the patient's condition.

Prevention: The preoperative prophylactic administration of cefuroxime may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (e.g., vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. Cefuroxime should usually be given one-half to one hour before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

Prophylactic administration is usually not required after the surgical procedure ends and should be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic administration of any antibiotic does not reduce the incidence of subsequent infections but will increase the possibility of adverse reactions and the development of bacterial resistance.

The perioperative use of cefuroxime has also been effective during open heart surgery for surgical patients in whom infections at the operative site would present a serious risk. For these patients it is recommended that cefuroxime therapy be continued for at least 48 hours after the surgical procedure ends. If an infection is present, specimens for culture should be obtained for the identification of the causative organism, and appropriate antimicrobial therapy should be instituted.

CONTRAINDICATIONS

Cefuroxime is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFUROXIME IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFUROXIME OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro.*

Mild cases of colitis may respond to drug discontinuation alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuation or when it is severe, oral vancomycin

growth of susceptible disease causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (e.g., vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. Cefuroxime should usually be given one-half to one hour before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

Prophylactic administration is usually not required after the surgical procedure ends and should be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic administration of any antibiotic does not reduce the incidence of subsequent infections but will increase the possibility of adverse reactions and the development of bacterial resistance.

The perioperative use of cefuroxime has also been effective during open heart surgery for surgical patients in whom infections at the operative site would present a serious risk. For these patients it is recommended that cefuroxime therapy be continued for at least 48 hours after the surgical procedure ends. If an infection is present, specimens for culture should be obtained for the identification of the causative organism, and appropriate antimicrobial therapy should be instituted.

CONTRAINDICATIONS

Cefuroxime is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFUROXIME IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFUROXIME OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*.

Mild cases of colitis may respond to drug discontinuation alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuation or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. Other causes of colitis should also be considered.

PRECAUTIONS

Although cefuroxime rarely produces alterations in kidney function, evaluation of renal status during therapy is recommended, especially in seriously ill patients receiving the maximum doses. Cephalosporins should be given with caution to patients receiving concurrent treatment with potent diuretics as these regimens are suspected of adversely affecting renal function.

The total daily dose of cefuroxime should be reduced in patients with transient or persistent renal insufficiency (see **DOSAGE AND ADMINISTRATION**), because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses.

As with other antibiotics, prolonged use of cefuroxime may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

As with other therapeutic regimens used in the treatment of meningitis, mild-to-moderate hearing loss has been reported in a few pediatric patients treated with cefuroxime sodium. Persistence of positive CSF (cerebrospinal fluid) cultures at 18-36 hours also has been noted with cefuroxime sodium injection, as well as with other antibiotic therapies; however, the clinical relevance of this is unknown.

Drug/Laboratory Test Interactions: A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with Clinitest® tablets) but not with enzyme-based tests for glycosuria (e.g., Tes-Tape®). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving cefuroxime.

Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of cefuroxime was found in standard laboratory tests.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in mice and rabbits at doses up to 60 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Since cefuroxime is excreted in human milk, caution should be exercised when sterile cefuroxime sodium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below 3 months of age have not been established. Accumulation of other members of the cephalosporin class in newborn infants (with resulting prolongation of drug half-life) has been reported.

ADVERSE REACTIONS

Sterile Cefuroxime Sodium is generally well tolerated. The most common adverse effects have been local reactions following IV administration. Other adverse reactions have been encountered only rarely.

Local Reactions: Thrombophlebitis has occurred with IV administration in 1 in 60 patients.

Gastrointestinal: Gastrointestinal symptoms occurred in 1 in 150 patients and included diarrhea (1 in 220 patients) and nausea (1 in 440 patients). Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see **WARNINGS**).

Hypersensitivity Reactions: Hypersensitivity reactions have been reported in fewer than 1% of the patients treated with cefuroxime and include rash (1 in 125). Pruritus, urticaria, and positive Coombs' test each occurred in fewer than 1 in 250 patients, and, as with other cephalosporins, rare cases of anaphylaxis, drug fever, erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome have occurred.

Blood: A decrease in hemoglobin and hematocrit has been observed in 1 in 10 patients and transient eosinophilia in 1 in 14 patients. Less common reactions seen were transient neutropenia (fewer than 1 in 100 patients) and leukopenia (1 in 750 patients). A similar pattern and incidence were seen with other cephalosporins used in controlled studies.

Hepatic: Transient rise in SGOT and SGPT (1 in 25 patients), alkaline phosphatase (1 in 50 patients), LDH (1 in 75 patients), and bilirubin (1 in 500 patients) levels has been noted.

Kidney: Elevations in serum creatinine and/or blood urea nitrogen and a decreased creatinine clearance have been observed, but their relationship to cefuroxime is unknown.

In addition to the adverse reactions listed above that have been observed in patients treated with cefuroxime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Vomiting, abdominal pain, colitis, vaginitis including vaginal candidiasis, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION**). If seizures associated with drug therapy should occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Altered Laboratory Tests: Prolonged prothrombin time, pancytopenia, agranulocytosis.

DOSAGE AND ADMINISTRATION

Dosage: ***Adults:*** The usual adult dosage range for cefuroxime is 750 mg to 1.5 grams every 8 hours, usually for 5 to 10 days. In uncomplicated urinary tract infections, skin and skin structure infections, disseminated gonococcal infections, and uncomplicated pneumonia, a 750-mg dose every 8 hours is recommended. In severe or complicated infections, a 1.5-gram dose every 8 hours is recommended.

In bone and joint infections, a 1.5-gram dose every 8 hours is recommended. In clinical trials, surgical intervention was performed when indicated as an adjunct to cefuroxime therapy. A course of oral antibiotics was administered when appropriate following the completion of parenteral administration of cefuroxime.

In life-threatening infections or infections due to less susceptible organisms, 1.5 grams every 6 hours may be required. In bacterial meningitis, the dosage should not exceed 3 grams every 8 hours. The recommended dosage for uncomplicated gonococcal infection is 1.5 grams given intramuscularly as a single dose at two different sites together with 1 gram of oral probenecid. For preventive use for clean-contaminated or potentially contaminated surgical procedures, a 1.5-gram dose administered intravenously just before surgery (approximately one-half to 1 hour before the initial incision) is recommended. Thereafter, give 750 mg intravenously or intramuscularly every 8 hours when the procedure is prolonged.

For preventive use during open heart surgery, a 1.5-gram dose administered intravenously at the induction of anesthesia and every 12 hours thereafter for a total of 6 grams is recommended.

Impaired Renal Function: A reduced dosage must be employed when renal function is impaired. Dosage should be determined by the degree of renal impairment and the susceptibility of the causative organism (see **TABLE 1**).

TABLE 1: DOSAGE OF CEFUROXIME IN ADULTS WITH REDUCED RENAL FUNCTION

Creatinine Clearance (mL/min)	Dose	Frequency
> 20	750 mg–1.5 grams	q8h
10–20	750 mg	q12h
< 10	750 mg	q24h*

*Since cefuroxime is dialyzable, patients on hemodialysis should be given a further dose at the end of the dialysis.

When only serum creatinine is available, the following formula2 (based on sex, weight, and

every 6 hours may be required. In bacterial meningitis, the dosage should not exceed every 8 hours. The recommended dosage for uncomplicated gonococcal infection is 1.5 grams given intramuscularly as a single dose at two different sites together with 1 gram of oral probenecid. For preventive use for clean-contaminated or potentially contaminated surgical procedures, a 1.5-gram dose administered intravenously just before surgery (approximately one-half to 1 hour before the initial incision) is recommended. Thereafter, give 750 mg intravenously or intramuscularly every 8 hours when the procedure is prolonged.

For preventive use during open heart surgery, a 1.5-gram dose administered intravenously at the induction of anesthesia and every 12 hours thereafter for a total of 6 grams is recommended.

Impaired Renal Function: A reduced dosage must be employed when renal function is impaired. Dosage should be determined by the degree of renal impairment and the susceptibility of the causative organism (see **TABLE 1**).

TABLE 1: DOSAGE OF CEFUROXIME IN ADULTS WITH REDUCED RENAL FUNCTION

Creatinine Clearance (mL/min)	Dose	Frequency
> 20	750 mg–1.5 grams	q8h
10–20	750 mg	q12h
< 10	750 mg	q24h*

*Since cefuroxime is dialyzable, patients on hemodialysis should be given a further dose at the end of the dialysis.

When only serum creatinine is available, the following formula[2] (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

$$\text{Males: } \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females: 0.85 x male value

Note: As with antibiotic therapy in general, administration of cefuroxime should be continued for a minimum of 48 to 72 hours after the patient becomes asymptomatic or after evidence of bacterial eradication has been obtained; a minimum of 10 days of treatment is recommended in infections caused by *Streptococcus pyogenes* in order to guard against the risk of rheumatic fever or glomerulonephritis; frequent bacteriologic and clinical appraisal is necessary during therapy of chronic urinary tract infection and may be required for several months after therapy has been completed; persistent infections may require treatment for several weeks; and doses smaller than those indicated above should not be used. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated.

Infants and Children Above 3 Months of Age: Administration of 50 to 100 mg/kg per day in equally divided doses every 6 to 8 hours has been successful for most infections susceptible to cefuroxime. The higher dosage of 100 mg/kg per day (not to exceed the maximum adult dosage) should be used for the more severe or serious infections.

In bone and joint infections, 150 mg/kg per day (not to exceed the maximum adult dosage) is recommended in equally divided doses every 8 hours. In clinical trials, a course of oral antibiotics was administered to children following the completion of parenteral administration of cefuroxime.

In cases of bacterial meningitis, a larger dosage of cefuroxime is recommended, 200 to 240 mg/kg per day intravenously in divided doses every 6 to 8 hours.

In children with renal insufficiency, the frequency of dosing should be modified consistent with the recommendations for adults.

Preparation of Solution and Suspension: The directions for preparing cefuroxime for both IV and IM use are summarized in Table 2.

For Intramuscular Use: Each 750 mg vial of cefuroxime should be constituted with 3 mL of sterile water for injection. Shake gently to disperse and withdraw completely the resulting suspension for injection.

For Intravenous Use: Each 750 mg vial should be constituted with 8 mL of sterile water for injection. Withdraw completely the resulting solution for injection.

Each 1.5 gram vial should be constituted with 16 mL of sterile water for injection, and the solution should be completely withdrawn for injection.

Each 750 mg and 1.5 gram infusion pack should be constituted with 100 mL of sterile water for injection, 5% dextrose injection, 0.9% sodium chloride injection, or any of the solutions listed under the intravenous portion of the **COMPATIBILITY AND STABILITY** section.

TABLE 2: PREPARATION OF SOLUTION AND SUSPENSION

Strength	Amount of Diluent to be Added (mL)	Volume to be Withdrawn	Approximate Cefuroxime Concentration (mg/mL)
750-mg Vial	3.0 (IM)	Total*	220
750-mg Vial	8.0 (IV)	Total	90
1.5-gram Vial	16.0 (IV)	Total	90
750-mg Infusion pack	100 (IV)	—	7.5
1.5-gram Infusion pack	100 (IV)	—	15

*Note: Sterile cefuroxime sodium, USP is a suspension at IM concentrations.

Administration: After constitution, cefuroxime may be given intravenously or by deep IM injection into a large muscle mass (such as the gluteus or lateral part of the thigh). Before injecting intramuscularly, aspiration is necessary to avoid inadvertent injection into a blood vessel.

Intravenous Administration: The IV route may be preferable for patients with bacterial septicemia or other severe or life-threatening infections or for patients who may be poor risks because of lowered resistance, particularly if shock is present or impending.

For direct intermittent IV administration, slowly inject the solution into a vein over a period of 3 to 5 minutes or give it through the tubing system by which the patient is also receiving other IV solutions.

For intermittent IV infusion with a Y-type administration set, dosing can be accomplished through the tubing system by which the patient may be receiving other IV solutions. However, during infusion of the solution containing cefuroxime, it is advisable to temporarily discontinue administration of any other solutions at the same site.

For continuous IV infusion, a solution of cefuroxime may be added to an IV infusion pack containing one of the following fluids: 0.9% sodium chloride injection; 5% dextrose injection; 10% dextrose injection; 5% dextrose and 0.9% sodium chloride injection; 5% dextrose and 0.45% sodium chloride injection; or 1/6 M sodium lactate injection.

Solutions of cefuroxime, like those of most beta-lactam antibiotics, should not be added to solutions of aminoglycoside antibiotics because of potential interaction.

However, if concurrent therapy with cefuroxime and an aminoglycoside is indicated, each of these antibiotics can be administered separately to the same patient.

Compatibility and Stability:

Intramuscular: When constituted as directed with sterile water for injection, suspensions of cefuroxime for IM injection maintain satisfactory potency for 24 hours at room temperature

Administration: After constitution, cefuroxime may be given intravenously or by deep IM injection into a large muscle mass (such as the gluteus or lateral part of the thigh). Before injecting intramuscularly, aspiration is necessary to avoid inadvertent injection into a blood vessel.

Intravenous Administration: The IV route may be preferable for patients with bacterial septicemia or other severe or life-threatening infections or for patients who may be poor risks because of lowered resistance, particularly if shock is present or impending.

For direct intermittent IV administration, slowly inject the solution into a vein over a period of 3 to 5 minutes or give it through the tubing system by which the patient is also receiving other IV solutions.

For intermittent IV infusion with a Y-type administration set, dosing can be accomplished through the tubing system by which the patient may be receiving other IV solutions. However, during infusion of the solution containing cefuroxime, it is advisable to temporarily discontinue administration of any other solutions at the same site.

For continuous IV infusion, a solution of cefuroxime may be added to an IV infusion pack containing one of the following fluids: 0.9% sodium chloride injection; 5% dextrose injection; 10% dextrose injection; 5% dextrose and 0.9% sodium chloride injection; 5% dextrose and 0.45% sodium chloride injection; or 1/6 M sodium lactate injection.

Solutions of cefuroxime, like those of most beta-lactam antibiotics, should not be added to solutions of aminoglycoside antibiotics because of potential interaction.

However, if concurrent therapy with cefuroxime and an aminoglycoside is indicated, each of these antibiotics can be administered separately to the same patient.

Compatibility and Stability:

Intramuscular: When constituted as directed with sterile water for injection, suspensions of cefuroxime for IM injection maintain satisfactory potency for 24 hours at room temperature and for 48 hours under refrigeration (5°C).

After the periods mentioned above any unused suspensions should be discarded.

Intravenous: When the 750-mg and 1.5-g vials are constituted as directed with sterile water for injection, the cefuroxime solutions for IV administration maintain satisfactory potency for 24 hours at room temperature and for 48 hours under refrigeration (5°C). More dilute solutions, such as 750 mg or 1.5 g plus 100 mL of sterile water for injection, 5% dextrose injection, or 0.9% sodium chloride injection, also maintain satisfactory potency for 24 hours at room temperature and for 7 days under refrigeration.

These solutions may be further diluted to concentrations of between 1 and 30 mg/mL in the following solutions and will lose not more than 10% activity for 24 hours at room temperature or for at least 7 days under refrigeration: 0.9% sodium chloride injection; 1/6 M sodium lactate injection; ringer's injection, USP; lactated ringer's injection, USP; 5% dextrose and 0.9% sodium chloride injection; 5% dextrose injection; 5% dextrose and 0.45% sodium chloride injection; 5% dextrose and 0.225% sodium chloride injection; 10% dextrose injection; and 10% invert sugar in water for injection.

Unused solutions should be discarded after the time periods mentioned above. Cefuroxime has also been found compatible for 24 hours at room temperature when admixed in IV infusion with heparin (10 and 50 U/mL) in 0.9% sodium chloride injection and potassium chloride (10 and 40 mEq/L) in 0.9% sodium chloride injection. Sodium bicarbonate injection, USP is not recommended for the dilution of cefuroxime.

Frozen Stability: Constitute the 750-mg or 1.5-g vial as directed for IV administration in Table 2. Immediately withdraw the total contents of the 750-mg or 1.5-g vial and add to a Baxter Viaflex® Mini-bag™ containing 50 or 100 mL of 0.9% sodium chloride injection or 5% dextrose injection and freeze. Frozen solutions are stable for 6 months when stored at -20°C. Frozen solutions should be thawed at room temperature and not refrozen. Do not force thaw by immersion in water baths or by microwave irradiation. Thawed solutions may be stored for up to 24 hours at room temperature or for 7 days under refrigeration (5°C).

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

As with other cephalosporins, cefuroxime powder, as well as solutions and suspensions, tends to darken, depending on storage conditions, without adversely affecting product potency.

HOW SUPPLIED

Sterile cefuroxie sodium, USP in the dry state should be stored between 15° and 30°C (59° and 86°F) and protected from light. Sterile cefuroxime sodium, USP is a dry, white to off-white powder supplied in vials and infusion packs as follows:

Sterile cefuroxime sodium equivalent to 750 mg or 1.5 grams cefuroxime per vial or infusion pack is supplied as follows:

NDC10515-125-01	750-mg vial (Tray of 25)
NDC10515-125-02	1.5-gram vial (Tray of 25)
NDC10515-125-03	750-mg infusion pack (Tray of 10)
NDC10515-125-04	1.5-gram infusion pack (Tray of 10)

Also available:

Pharmacy Bulk Package containing 7.5 grams cefuroxime per vial.

NDC10515-124-05	7.5-gram vial Pharmacy Bulk Package (Tray of 10)

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES

1. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Susceptibility Testing.* Third Informational Supplement. NCCLS Document M100-S3, Vol. 11, No. 17. Villanova, Pa: NCCLS; 1991.
2. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976; 16:31–41.

MANUFACTURED BY:
G.C. Hanford Mfg. Co.
Syracuse, NY 13201

INS11339 01.....February 1996

[redacted]

[redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064125

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. #4

2. AADA #64-125

3. NAME AND ADDRESS OF APPLICANT
G.C. Hanford Manufacturing Company
Attention: Carl E. Fuller
304 Oneida Street
P.O. Box 1017
Syracuse, NY 13201

4. LEGAL BASIS FOR SUBMISSION
21 CFR §442.218a (442.18a)

Reference drug: Zinacef® (sterile cefuroxime sodium) manufactured by Glaxo Pharmaceuticals

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Sterile Cefuroxime Sodium

#64-124: 7.5 g/100 mL Pharmacy Bulk package
#64-125: 750 mg and 1.5 g in 10 mL and 100 mL piggyback vials

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original application: 3/31/94
FDA letter (Refusal to File) 4/20/94 requesting information
Amend 5/11/94
Amend 8/25/95 to N/A letter 9/2/94
Amend 4/23/96 to N/A letter 2/8/96
Amend 5/23/96 (Telephone): labeling
Amend 10/15/96 to N/A letter 7/16/96
Amendments 8/29/96 and 1/23/97 (Bio)

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

(b)4 - Confidential Business

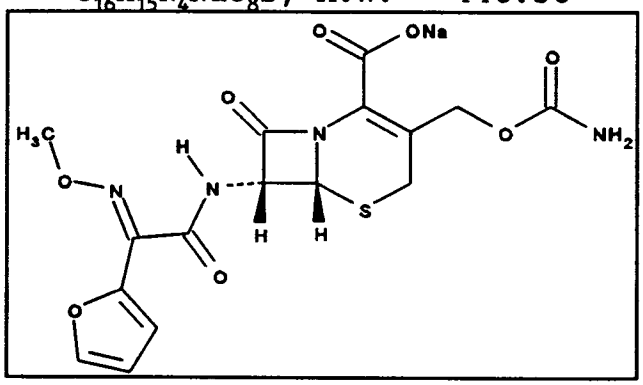
13. DOSAGE FORM
Sterile powder for injection

14. POTENCY
See under #7

15. CHEMICAL NAME AND STRUCTURE

Cefuroxime Sodium USP

$C_{16}H_{15}N_4NaO_8S$; M.W. = 446.36



Sodium (6R,7R)-7-[2-(2-furyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7^2-(*Z*)-(*O*-methyloxime), carbamate (ester). CAS [56238-63-2]

16. RECORDS AND REPORTS
N/A

17. COMMENTS

In N/A letter 7/16/96 (CR #3), Hanford's CGMP-related issues were cited, as well as bio (for #64-125) and sample analysis issues. Sample validation for both AADA #64-124 and 64-125 is found to be acceptable (8/5/96). Since both applications share a common package insert, they can not be approved independently. In Firm's amendment 10/15/96, Firm states that they have resolved the CGMP issues and requests to schedule a pre-approval inspection. A update EER is requested (10/23/96). Bio issue for #64-125 is now found acceptable (see Bio letter dated 3/26/97).

18. CONCLUSIONS AND RECOMMENDATIONS
Approval recommended (pending on EER).

19. REVIEWER:
Maria C. Shih

DATE COMPLETED:
3/31/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064125

BIOEQUIVALENCE REVIEW(S)

MAY 28 1996

Cefuroxime Sodium
750 mg/10 ml IM/IV vial
AADA 64-125
Reviewer: Pradeep M. Sathe, Ph.D.
WP # 64125W.196

G.C. Hanford Manufacturing Co.
Syracuse, New-York-13201
Submission Date:
January 19, 1996

REVIEW OF AN AMENDMENT

THE OBJECTIVE : The amendment consists of G.C. Hanford's request for a bio-study waiver for its 750 mg/10 ml IV/IM vial formulation.

REVIEWER'S OPINION : Based on the regulations and precedence, the bio-study waiver may not be granted.

The opinion is based on the following review :

BACKGROUND : The firm (G.C.Hanford) had submitted application for the Cefuroxime Sodium vial on May 13, 1994. OGD found the application deficient. The firm was made aware of the chemistry and bio-equivalency deficiencies. In a letter dated September 29, 1995, the firm was asked to carry out a bioequivalency study for its 750 mg formulation's IM indication. Responding to that letter, the firm has come up with a solubility and dissolution data comparing the test (G.C. Hanford) and the reference (Zinacef^{R} by Glaxo) formulations.

THE ISSUE : Cefuroxime Sodium is an anti-infective with a water solubility of 170 mg activity per ml. The 750 mg/10 ml Cefuroxime Sodium formulation can be used as a intra-venous (with 8 ml reconstitution) or intra-muscular (with 3 ml reconstitution) with the sterile water for injection. For intra-venous mode, the formulation is completely soluble in water. For the intra-muscular mode of administration, however, the 750 mg formulation is not completely soluble in 3 ml diluent (sterile water for injection). Upon reconstitution for intra-muscular application, only 68-72% of Cefuroxime content is in solution (Attachment I). The reasons for not granting the waiver are as follows:

1. The formulation being only partially soluble with 3 ml reconstitution, is not completely covered by CFR 320.22 (1)(i) for the eligibility of a bio-study waiver.

2. Previously in January 1985, another firm has conducted a bio-equivalency study for it's intra-muscular indication. We thus have a precedence. Some other formulations with similar background (iron-dextran suspension for intra-muscular use) also were asked to conduct a study indicating a policy consistency.

3. Without a bioequivalency study, the agency cannot ascertain that the rate and extent of absorption of the two formulations are similar.

4. The hand-shaking dissolution method is not validated and may not be consistent for all formulations.

COMMENT :

It should be clearly understood that the law prohibits the agency from knowingly approving a product unless it is determined to be bioequivalent to the reference formulation. In this case, the reconstituted formulation (for the intra-muscular use), is not a perfect solution and bioequivalency has not been demonstrated.

RECOMMENDATIONS :

1. The Division of Bioequivalence feels that the information submitted by G.C.Hanford does not demonstrate that Cefuroxime Sodium 750 mg/10 ml vial for the intra-muscular use, falls under 21 CFR section 320.22 (1)(i) of the bioavailability/bioequivalence regulations. The waiver request of in-vivo bioequivalence study for 750 mg/10 ml vial for IM use is denied.

2. The firm should be asked to submit a protocol for the bioequivalency study comparing the 750 mg/10 ml vial after 3 ml reconstitution (with the sterile water for injection) for the test (G.C. Hanford) and the reference Zinacef[R] by Glaxo-Wellcome, formulations.

(Note : The firm has already submitted a study prot[redacted]iew on April 19, 1996).

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RT Initialed by YCHuang[redacted]
FT Initialed by YCHuang[redacted] 5/25/96

Concur: Keith Chan, Ph.D[redacted] 25/96
Director,
Division of Bioequivalence.

cc: AADA 64-125 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-652 (YCHuang, Sathe), Drug file, Division file.

Attachment I

Table IV

Cefuroxime Sodium Dissolution Study

	Dissolution Time in Seconds									
	30	60	90	120	150	180	210	240	270	300
150 mgA/mL (450 mgA/vial)										
Lot #										
BF770	Y	Y								
BF279	N	Y								
5H70949	Y	Y								
95-P07	Y	Y								
95-P08	Y	Y								
160 mgA/mL (480 mgA/vial)										
Lot #										
BF770	N	Y								
BF279	N	Y								
5H70949	Y	Y								
95-P07	Y	Y								
95-P08	Y	Y								
170 mgA/mL (510 mgA/vial)*										
Lot #										
BF770	N	N	Y							
BF279	N	N	Y							
5H70949	N	Y	Y							
95-P07	N	Y	Y							
95-P08	N	Y	Y							
180 mgA/mL (540 mgA/vial)**										
Lot#										
BF770	N	N	N	N	N	N	N	N	N	N
BF279	N	N	N	N	N	N	N	N	N	N
5H70949	N	N	N	N	N	N	N	N	N	N
95-P07	N	N	N	N	N	N	N	N	N	N
95-P08	N	N	N	N	N	N	N	N	N	N

Glaxo - Lot #'s BF770 & BF279
Marsam - Lot # 5H70949
Hanford - Lot #'s 95-P07 & 95-P08

Y = Soluble
N = Not completely soluble

* Equivalent to 68% of 750 mg target activity
**Equivalent to 72% of 750 mg target activity

Sample Weights:

The actual sample weights used in the solubility equivalence study are provided in Table III for informational purposes. Slightly higher weights were used for the Marsam and Hanford lots to produce equivalent Cefuroxime target activities per vial. Equivalent solubility profiles were obtained in all cases even with these marginally higher sample weights.

Table III

Test Lot Weights

Source:	Glaxo	Glaxo	Marsam	Hanford	Hanford
Lot Number:	BF770	BF279	5H70949	95-P07	95-P08
Target Activity*	Sample Weight (mg)				
450 mgA/vial	493.4	492.5	501.5	504.1	500.0
480 mgA/vial	525.8	525.0	535.1	538.1	533.2
510 mgA/vial	559.2	557.1	568.2	570.8	567.3
540 mgA/vial	592.5	590.0	601.0	605.3	600.4

* 450, 480, 510, and 540 mgA/vial corresponds to 150, 160, 170, and 180 mg/mL for a 3.0 mL constitution volume.

Results:

Dissolution Study:

The results of the solubility equivalence study is shown in Table IV below. The Glaxo, Marsam and Hanford samples were all soluble at 170 mg of Cefuroxime Activity per mL (170mgA/mL) within 90 seconds of shaking. None of the samples tested were completely in solution at the 180 mgA/mL level after 5 minutes of shaking.

The solubility profiles of the Glaxo, Marsam, and Hanford samples tested are equivalent.

Solubility - 750mg/10mL Presentation:

The 170 & 180 mgA/mL levels correspond to 510 & 540 mg of Cefuroxime activity per vial, respectively. Based upon a target activity of 750 mg per vial, the 510 mgA/vial level corresponds to 68 % of the target activity (510 ÷ 750 × 100) and the 540 mgA/vial level corresponds to 72 % of the target activity (540 ÷ 750 × 100).

Based on the data provided in Table IV, between 68 and 72 % of the Cefuroxime target activity in Glaxo's, Marsam's and Hanford's 750mg/10mL IM suspension is in solution when constituted with 3.0 mL of SWFI.

In addition, complete solution was obtained when a total of 5.0 mL of SWFI was added to Hanford lot 95-P07 within 30 seconds of shaking. Therefore, the remaining undissolved material, after 3.0 mL of constitution with SWFI, is soluble in 2.0 mL of additional diluent.

Conclusion:

Cefuroxime Sodium (from Glaxo, Marsam, and Hanford finished products) has been shown to be highly soluble in water (> 170 mg of Cefuroxime activity per mL of SWFI). The dissolution study indicates that 68 to 72 percent of the 750 mg/vial label claim for the 750mg/10mL IM suspension presentations from Glaxo, Marsam, and Hanford is in solution when constituted with 3.0 mL of SWFI. The remaining suspension is completely soluble with the addition of only 2.0 mL of SWFI. The dissolution study also shows that the Glaxo, Marsam and Hanford materials have equivalent solubility profiles.

Furthermore, Cefuroxime Sodium Sterile, USP finished product dissolution profiles would not be affected by processing as in the case of a tablet, capsule, or suspension containing additional excipients. Also it is not a low or totally insoluble suspension whose bio-equivalence would be unpredictable. Cefuroxime Sodium Sterile, USP is a well-characterized compound filled into vials with no added excipients to affect its high solubility, its solubility characteristics, or the solubility equivalence of Glaxo, Marsam, and Hanford finished products.

In this exceptional case the data and scientific rationale support our request for a bio-equivalence waiver.

AADA 64-125

MAR 26 1997

G. C. Hanford Manufacturing Co.
Attention: Carl E. Fuller
304 Oneida Street
Post Office Box 1017
Syracuse NY 13201

Dear Sir:

Reference is made to your abbreviated antibiotic application submitted pursuant to Section 507 of the Federal Food, Drug and Cosmetic Act for Sterile Cefuroxime Sodium USP, 750 mg/10 mL IM/IV vial.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAR 18 1997

Sterile Cefuroxime Sodium
750 mg/10 mL and 100 mL
1.5 g/20 mL and 100 mL vials
AADA # 64-125
Reviewer: Man M. Kochhar
64125S.1096

G.C.Hanford Manufacturing Co
Syracuse, New York
Submission Date:
October 16, 1996

Review of a Bioequivalence Study

I. BACKGROUND

Cefuroxime is a semisynthetic, broad spectrum, cephalosporin antibiotic for parenteral administration.

The mean peak serum concentration for cefuroxime is reported to be 27 mcg/mL following a 750 mg intramuscular dose in normal volunteers. The peak occurred at approximately 45 minutes (range, 15 to 60 minutes). The serum half-life is about 80 minutes.

II. OBJECTIVE

The objective of this study is to assess the bioequivalence of G.C.Hanford's cefuroxime sodium 750 mg powder for injection formulation, compared with Glaxo Wellcome's Zinacef 750 mg powder for injection, following a single 750 mg intramuscular dose under fasting conditions.

III. IN-VIVO STUDY

The Purpose of this study is to assess the bioequivalence of two formulations of cefuroxime 750 mg/10 mL for injection by Hanford, compared with Zinacef 750 mg/10 mL for injection by Glaxo Wellcome when given under fasting conditions.

(b)4 - Confidential Business

IV. STUDY DESIGN

The study was designed as a randomized, single dose, two-way crossover bioequivalence study in healthy volunteers under fasting conditions.

Number of Subjects: 28 healthy male volunteers were enrolled in the study. 27 subjects completed the study. Subject #1 did not show up for period 2.

Treatments: A. Test: 1 x 750 mg/10 mL vial cefuroxime injection (lot # 95-P07) into the right gluteal muscle.

Expiration Date: n/a

B. Reference: 1 x750 mg/10 mL vial Zinacef injection (Glaxo, lot # BF977) into the right gluteal muscle.

Expiry: 10/97.

Blood Samples: Samples were collected in Vacutainers before dosing (7 mL) and at 10, 20, 30, 45 and 60 minutes; 1.33, 1.67, 2, 3, 4, 5, 6, 8, 10 and 12 hours after dosing. Blood sat at room temperature until fully clotted. Samples were collected and processed under yellow lighting. The serum then was seprated by centrifugation and stored for analysis.

Fasting/Meals: Fast for 8 hours before dosing and 2 hours after dosing. Light breakfast was served 2 hours after dosing, lunch 5-6 hours and dinner 10-11 hours after dosing.

Housing: From 10 hours before dosing until after the collection of 12 hours blood sample.

Washout Period: 3 days between doses.

Analytical Method: (b)4 - Confidential Business

Subject Screening:

Study had used male and female volunteers between the ages of 19-60, and within ±10% of their frame and size according to Metropolitan Life Insurance Company Bulletin,1983. The subjects were selected for this study after i) physical examination, ii) medical and complete laboratory tests (blood chemistry, hematology, urinalysis, etc.). The volunteers were instructed not to take any prescription medications and/or OTC preparations for at least one week prior to the start and until the end of the study. The volunteers were not allowed to drink alcoholic beverages or caffeine-containing products for 24 hours prior to dosing and during the periods when blood samples being collected.

Each subject signed a written informed consent form.

Pharmacokinetic and Statistical Analysis:

Serum concentration-time profiles of cefuroxime were analyzed pharmacokinetically and statistically to evaluate relative bioavailability of test product to reference product. Significance of differences due to treatments, phase, dosing and sequence were evaluated for serum cefuroxime concentrations at each sampling time and Cmax, Tmax, Kel, t1/2 and AUC by ANOVA using SAS (GLM procedure).The power to detect 20% differences between formulations (t-test method), and 90% confidence intervals (two,one-sided t-test) were calculated for each major pharmacokinetic parameter.

ASSAY VALIDATION

(b)4 - Confidential Business

[redacted]

(b)4 - Confidential Business

[redacted]

DATA ANALYSIS:

Individual analysis of variance (ANOVA with factors including drug, phase, sequence and subjects within sequence) was carried out to compare formulations at each sampling time, AUC (0-t), AUC (inf.), Cmax, Tmax, t1/2 and Kel. All ANOVAs were performed with SAS General Linear Models Procedures (GLM). 90% confidence intervals (two one-sided t-test method) were calculated for cefuroxime pharmacokinetic parameters. For all analyses, effects were considered statistically significant if the probability associated with 'F' was less than 0.05.

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

Of the 28 subjects enrolled in the study 27 completed the crossover. Subject # 1 did not show up for the second phase.The serum samples from 27 subjects were assayed for cefuroxime as per the protocol. The study was completed with no major protocol violations. The results of the study comparing the bioavailability of cefuroxime are given in Table 1 and 2. The mean serum cefuroxime concentrations are given in Figure 1.

TABLE 1

Mean Serum Concentration of Cefuroxime (N=27)

Time (hours)	Hanford's Cefuroxime Lot # 95P07 mcg/mL (CV%)	Glaxo's Zinacef Lot # BF977 mcg/mL (CV%)	T/R
0	0 (-)	0 (-)	0.0
0.17	3.7 (87)	4.6 (62)	0.80
0.33	8.4 (59)	10.1 (39)	0.83
0.50	12.3 (44)	13.8 (31)	0.89
0.75	15.6 (35)	17.7 (26)	0.88
1	17.5 (29)	19.1 (22)	0.92
1.33	18.4 (23)	19.5 (20)	0.94
1.67	18.5 (21)	19.2 (18)	0.96
2	17.6 (21)	18.0 (18)	0.98
3	14.7 (23)	13.3 (23)	1.10
4	10.5 (27)	8.7 (27)	1.20
5	7.0 (36)	5.6 (31)	1.25
6	4.4 (42)	3.5 (37)	1.25
8	1.7 (49)	1.4 (48)	1.21
10	0.6 (63)	0.5 (72)	1.20
12	0.2 (114)	0.1 (152)	2.00

Table 2

A Summary of Cefuroxime Pharmacokinetic Parameters for 27 subjects

Parameters	Hanford's Cefuroxime	Glaxo's Zinacef	T/R	90% Confidence Interval
AUC_{0-t} mcg.hr/mL	81.16 (20)	76.53 (17)	1.06	
AUC_{0-inf} mcg.hr/mL	81.91 (20)	77.28 (17)	1.06	
C_{max} mcg/mL	19.67 (23)	20.54 (18)	0.96	
T_{max} (hours)	1.63 (37)	1.40 (30)	1.16	
$t_{1/2}$ (hours)	1.40 (14)	1.36 (13)	1.03	
K_{el} (1/hour)	0.5032 (13)	0.5183 (13)	0.97	

			Geometric Mean Ratio	
Ln AUC_{0-t} mcg.hr/mL	4.38 (5)	4.32 (22)	1.06	103; 109
Ln AUC_{inf} mcg.hr/mL	4.38 (5)	4.33 (22)	1.06	102; 109
Ln C_{max} mcg/mL	2.95 (7)	3.01 (18)	0.95	89; 101

The cefuroxime AUC_{0-t} and AUC_{0-inf} produced by Hanford's formulation were 6% higher and 5.9% higher respectively than the values for the reference drug. The C_{max} was 4.2% lower than the reference. T_{max} was 16.4% higher for the test drug. $t_{1/2}$ and K_{el} values differ only by less than 3%. ANOVA performed on the serum cefuroxime concentration data at each of the fifteen sampling times detected no statistically significant differences at any time point between the two formulations. The firm did calculate Ln AUC and Ln Cmax for cefuroxime and the 90% confidence intervals for log-transformed parameters were 103 to 109 for Ln AUC0-t, 102 to 109 for Ln AUCinf, and 89 to 101 for Ln Cmax.

The 90% confidence interval for cefuroxime for AUC_{0-t} and AUC_{0-inf} and C_{max} were well within ±20% limits set for defining product bioequivalence, in a fasting study.

There were minor adverse events reported; headache, stomachache, itching, nausea, shaky, fainted. There were no serious adverse effects which required dropping any subjects from the study or required therapeutic medical intervention.

On the basis of fasting in vivo bioavailability data it is determined that Hanford's cefuroxime sodium 750 mg/10 mL injections and Glaxo's Zinacef 750 mg/10 mL injections are bioequivalent under fasting conditions.

COMMENTS:

1. The study was conducted in 27 healthy volunteers comparing the serum concentrations from Hanford's cefuroxime 750 mg/10 mL injections to that of reference Zinacef 750 mg/10 mL injections manufactured by Glaxo Wellcome. The cefuroxime AUC_{0-t}, AUC_{0-inf}, C_{max} of the Hanford's formulation were 6% higher, 5.9% higher, and 4.2% lower respectively than the corresponding Glaxo's reference values. ANOVA performed on the serum cefuroxime concentration

data detected no statistically significant differences at any point between two formulations. These results indicate that the test drug is bioequivalent to the reference product under fasting conditions. The ratios of individual pharmacokinetic parameters are given in Table 3.

2. Due to mistake during study conducted for Period 1(45 minute blood draw not collected), an additional study period (Period 3) was added to the study. The pharmacokinetic data was analyzed from study Period 2 and 3 only. Serum samples from all subjects who completed Period 2 and 3 of the study was assayed for cefuroxime sodium.

3. Although a third period was added to the study, the study is treated as a two period crossover study for the purpose of pharmacokinetic parameters. During the Period 1, subjects 1-15 missed their 0.75 hour blood collection. Subsequent blood collections were discontinued following the 5 hour sample. Thus, the 6, 8, 10, and 12 hours samples were not collected for these subjects. All samples were collected as scheduled for subjects 16-26 during Period 1.

4. All subjects were requested to return for a third study Period, which would be a repeat os study Period 1. It was determined that not all 26 original subjects were able to return for a third period. As a result, some of the subjects completed the study as defined by the original protocol (Period 1 and 2) and rest of the subjects completed the study as follows:

Subject No.	Study Period	
1	None	did not complete Period 2
2-15	II III	
16-26	I II	
27,28	II III	

5. We reanalyze the data as three-periods crossover and our results are as follows:

AUC0-t	T/R = 0.9475	and CI 92.08% to 97.50%
AUCinf	T/R = 0.948	and CI 92.15% to 97.58%
Cmax	T/R = 1.05	and CI 98.57% to 112.4%

6. Analysis of variance indicated no statistical significant treatment differences or group-by-sequence effect for AUC and Cmax for cefuroxime. The 90% confidence intervals were well within the limits of ±20%.

7. The validation studies conducted by the sponsor for cefuroxime are acceptable to the Division of Bioequivalence.

8. The <u>in vivo</u> fasting bioequivalence study is acceptable.

DEFICIENCY: None

RECOMMENDATIONS:

1. The fasting bioequivalence study conducted by G.C.Hanford Manufacturing Company on its Cefuroxime 750 mg/10 mL injection, lot # 95-P07, comparing it to Zinacef 750 mg/10 mL injection, lot # BF977 manufactured by Glaxo Wellcome Inc. has been found acceptable by the Division of Bioequivalence. The study demonstrates that under fasting conditions the Hanford's Cefuroxime 750 mg/10 mL injection is bioequivalent to the reference product, Zinacef 750 mg/10 mL injection manufactured by Gaxo Wellcome.

2. From the bioequivalence point of view, the firm has met the requirements for in vivo bioequivalence study, and therefore, the study is acceptable.

The firm should be informed of the recommendations.

/S/

Man M.Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

/S/ 3/12/97

Ramakant M. Mhatre, Ph.D.
Chief, Branch III
Division of Bioequivalence

Concur: /S/ Date: 3/18/97

Nicholas M. Fleischer, Ph.D
Acting Director
Division of Bioequivalence

MMKochhar/mmk/12-13-96; 1-8-97; 1-27-97; 3-10-97; 64-125

Table 3

Individual and Mean Pharmacokinetic Parameter Value Ratios for Serum Cefuroxime Concentrations

Treatment A versus Treatment B

Subject Number	Treatment Sequence	Parameters Cmax	Tmax	AUC(0-t)	AUC(0-inf)	Kel	T1/2el
2	AB	1.105	0.667	[redacted]	[redacted]	[redacted]	[redacted]
3	BA						
4	BA						
5	BA						
6	BA						
7	AB						
8	BA						
9	BA						
10	BA						
11	AB						
12	AB						
13	BA						
14	AB						
15	AB						
16	BA						
17	BA						
18	AB						
19	AB						
20	BA						
21	BA						
22	BA						
23	AB						
24	BA						
25	AB						
26	AB						
27	AB						
28	BA						
Mean		1.069	0.934	0.950	0.951	1.036	0.975
S.D.		0.202	0.376	0.082	0.083	0.105	0.101
C.V.(%)		18.871	40.220	8.649	8.688	10.092	10.388
S.E.M.		0.039	0.072	0.016	0.016	0.020	0.019
N		27.000	27.000	27.000	27.000	27.000	27.000
Minimum		0.756	0.250	0.806	0.808	0.823	0.814
Maximum		1.502	2.000	1.119	1.118	1.229	1.215

Ratio = Zinacef(R) (Sterile Cefuroxime Sodium) 750 mg / Sterile Cefuroxime Sodium, 750 mg

Table 3

Individual and Mean Pharmacokinetic Parameter Value Log-Ratios for Serum Cefuroxime Concentrations

Treatment A versus Treatment B

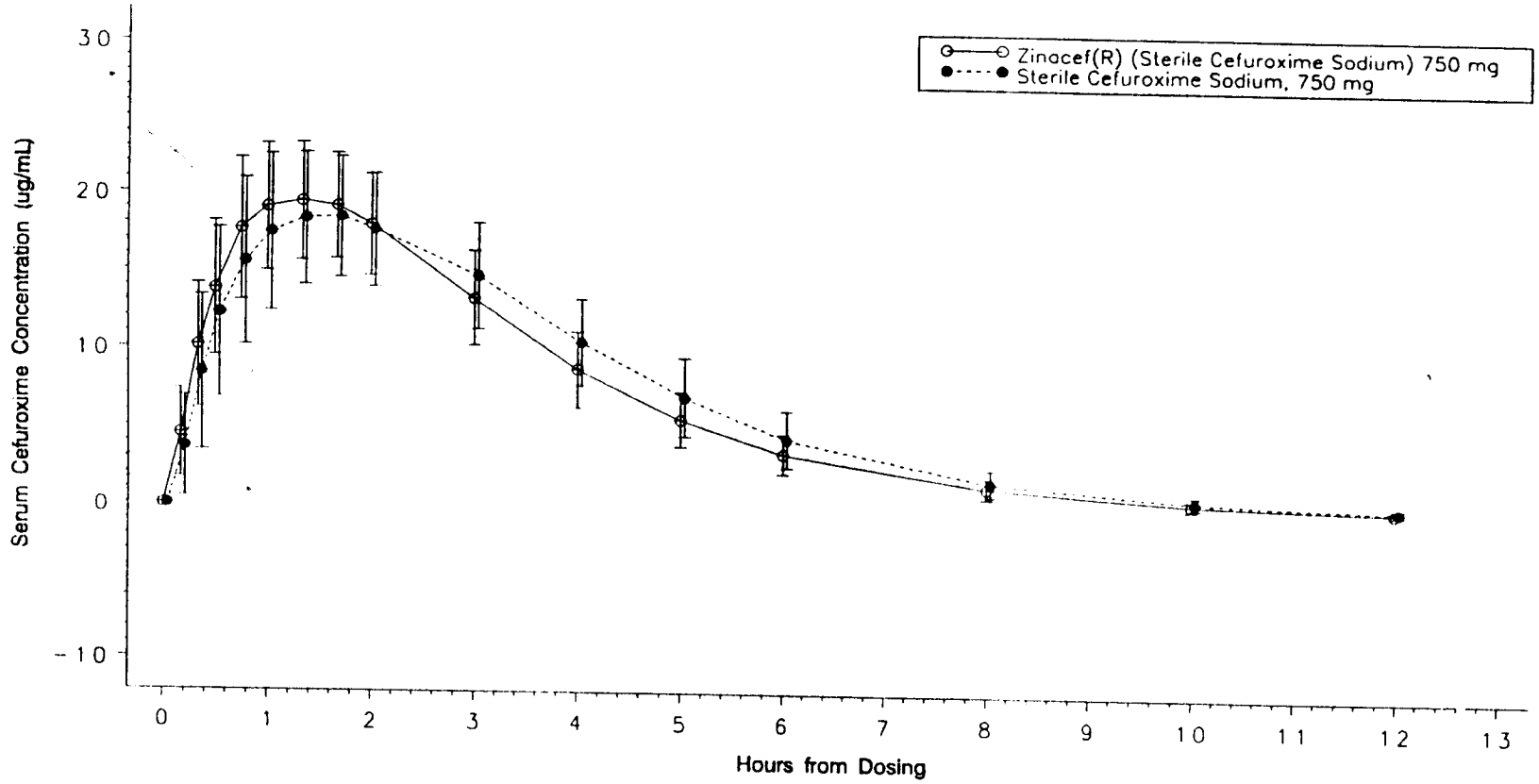
Subject Number	Treatment Sequence	Parameters					
		Cmax	Tmax	AUC(0-t)	AUC(0-inf)	Kel	T1/2el
2	AB						
3	BA						
4	BA						
5	BA						
6	BA						
7	AB						
8	BA						
9	BA						
10	BA						
11	AB						
12	AB						
13	BA						
14	AB						
15	AB						
16	BA						
17	BA						
18	AB						
19	AB						
20	BA						
21	BA						
22	BA						
23	AB						
24	BA						
25	AB						
26	AB						
27	AB						
28	BA						
Mean		0.049	-0.147	-0.055	-0.054	0.030	-0.030
S.D.		0.193	0.418	0.086	0.086	0.102	0.102
C.V.(%)		391.15	-284.9	-156.9	-161.1	337.73	-337.7
S.E.M.		0.037	0.081	0.017	0.017	0.020	0.020
N		27.000	27.000	27.000	27.000	27.000	27.000
Minimum		-0.280	-1.386	-0.216	-0.213	-0.194	-0.206
Maximum		0.407	0.693	0.112	0.112	0.206	0.194

Log-Ratio = LN(Ratio)

Figure 1

Mean (S.D.) Serum Cefuroxime Concentrations versus Time

Linear Scale



Symbols are offset for easier viewing